

**CLEAN VERSION OF AMENDED CLAIMS:**

2. (Amended) The method of claim 41, wherein the replication defective hepadnavirus particles are human hepatitis B virus particles
3. (Amended) The method of claim 41, wherein the heterologous gene replaces sequences of the S-gene.
4. (Amended) The method of claim 41, wherein the heterologous gene replaces a region of the S-gene under control of the endogenous S-promoter.
5. (Amended) The method of claim 41, wherein the heterologous gene is inserted such that one of an authentic AUG codon of the S-gene or its nucleotides encoding further amino acids of the S-protein are fused in frame to the 5' end of the heterologous gene.
6. (Amended) The method of claim 41, wherein the heterologous gene encodes a modulating agent.
8. (Amended) The method of claim 7, wherein the cytokine is selected from the group consisting of IFN $\alpha$ , IFN $\beta$ , IFN $\gamma$ , TNF $\alpha$ , IL-12 and IL-18.

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33. (Amended) A replication defective hepadnavirus particle, wherein a region of a pre-S and S-gene of the hepadnavirus genome have been deleted and replaced by a heterologous gene such that the sequences for RC and RII that are essential for producing reverse transcriptase are retained.

34. (Amended) The replication defective hepadnavirus particle of claim 33, wherein the heterologous gene is a cytokine

36. (Amended) The replication defective hepadnavirus particle of claim 34, wherein the cytokine is selected from the group consisting of  $\text{TNF}\alpha$ ,  $\text{IFN}\beta$ , IL-18,  $\text{IFN-}\gamma$  and IL-12.

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37. (Amended) A pharmaceutical composition comprising:

- a replication defective hepadnavirus with a region of its pre-S-genes deleted and replaced with a heterologous gene such that the sequences of the RC r RII that are essential for producing reverse transcriptase are retained, and
- a pharmaceutically acceptable carrier.

38. (Amended) The pharmaceutical composition of claim 37 further comprising: a helper virus.

39. (Amended) A method of producing replication defective hepadnavirus particles at a titer suitable for infecting hepatocytes comprising:

- co-transfecting hepatocyte cells of a hepatoma cell line with:
  - (i) replication defective hepadnavirus constructs, wherein a region of one of a pre S or an S-gene of the hepadnavirus DNA has been replaced with a gene encoding a heterologous gene while retaining one of an RC or RII signal, such that the expression of the gene encoding a cytokine is regulated by regulatory sequences of the S-gene; and
  - (ii) a helper construct for transcomplementing lacking viral gene products;
- culturing the hepatocytes until infectious viral particles are produced; and
- recovering the infectious particles.

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**IN THE CLAIMS:**

**Cancel** claims 9-32 without prejudice to the reentry of the same subject matter at any later time.

**Add** the following claims:

41. (New) The method of claim 39, wherein the cell line is stably transfected with the helper construct and serves as a packaging cell line.
42. (New) A method for producing replication defective recombinant hepadnavirus particles capable of expressing a heterologous gene in hepatocytes comprising:
- replacing an S-gene in a hepatitis B virus genome with the heterologous gene such that the expression of the heterologous gene is regulated by an S-promoter;
  - producing a replication deficient hepadnavirus by means of a helper plasmid transcomplementing viral gene products such that the lacking viral gene products are present;
  - infecting hepatocytes with the recombinant hepadnavirus, whereby the heterologous gene is delivered into the hepatocyte and expressed in the hepatocyte.
43. (New) A recombinant HBV genome, wherein an S-gene in the HBV genome is deleted and replaced by a heterologous gene and wherein the

sequences for RC and RII that are essential for reverse transcription are retained.

44. (New) The recombinant HBV genome of claim 43, wherein the heterologous gene is under the control of the endogenous S promoter

45. (New) The recombinant HBV genome of claim 43, wherein the heterologous gene is an immunomodulator.

46. (New) The recombinant HBV genome of claim 43, wherein the heterologous gene is a cytokine.

47. (New) The recombinant HBV genome of claim 44, wherein the immunomodulator is selected from the group consisting of IFN $\alpha$ , IFN $\beta$ , IFN $\gamma$ , TNF $\alpha$ , IL-18 or IL-12.

48. (New) The recombinant HBV genome of claim 43, wherein the heterologous gene is a chemokine.

49. The replication defective hepadnavirus particle of claim 33, wherein expression of the gene is regulated by regulatory sequences of the S-gene.

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50. The replication defective hepadnavirus particle of claim 34, wherein the heterologous gene is a chemokine

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